

CHAPTER

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Nosocomial Pneumonia – Recent Guidelines for Management

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Introduction

Nosocomial pneumonia (NP) is the second most common nosocomial infection after urinary tract infection but is the leading cause of mortality due to hospital acquired infections. The initial 1996 American Thoracic Society (ATS) guidelines on nosocomial pneumonia has been updated by the joint committee of the ATS and Infectious Disease Society of America (IDSA) and published in 2005 which recognises the new entity called health care associated pneumonia, describes strategy for clinical and bacteriological diagnosis and approach for management.¹

Definition

Nosocomial pneumonia or Hospital Acquired Pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after hospital admission, which was not incubating at the time of admission. NP also includes the subset of ventilator associated pneumonia (VAP). VAP refers to pneumonia developing more than 48 to 72 hours after endotracheal intubation. HCAP (Health Care Associated Pneumonia) has also been included in the spectrum of NP. Patients at risk for HCAP include the following :

a. Any patient who was hospitalised in an acute care hospital for 2 or more days within 90 days of the infection;

- b. resided in a nursing home or long term care facility,
- c. received recent intravenous antibiotic therapy, dialysis, chemotherapy, or wound care within the past 30 days of the current infection.

These patients are at risk of multi drug resistant (MDR) bacterial pathogens, so they are considered as NP rather than community acquired pneumonia.

Epidemiology

Available data suggests that it occurs at a rate of 5 to 10 cases per 1000 hospital admissions, with the incidence increasing by as much as 6 to 20 fold in mechanically ventilated patients.^{2,3} The exact incidence may vary widely depending on the case definition of pneumonia and the population being evaluated. For example, the incidence of VAP may be upto two times higher in patients diagnosed by qualitative or semi-quantitative sputum cultures compared with quantitative cultures of lower respiratory tract secretion. VAP recurs in 9-27% of all intubated patients. The risk of VAP is highest early in the course of hospital stay, and is estimated to be 3% day during the first five days of ventilation, 2% day during days 5-10 of ventilation, and 1% day after this. Because most mechanical ventilation is short term, approximately half of all episodes of

Table 1 : Risk factors for MDR pathogens causing Nosocomial Pneumonia

1. Antibiotic therapy in preceding 90 days.
2. Current hospitalisation of 5 days or more (late onset pneumonia).
3. High frequency of antibiotic resistance in the community or in the hospital unit.
4. Presence of risk factor for HCAP
 - Hospitalisation for 2 days or more in the preceding 90 days.
 - Residence in a nursing home or extended care facility.
 - Home infusion therapy
 - Chronic dialysis within 30 days.
 - Home wound care.
 - Family member with multidrug resistant pathogens.
5. Immunosuppression disease or therapy.

VAP occur within the first 4 days of mechanical ventilation.

The crude mortality rate for HAP may be as high as 30 to 70%, but many of these critically ill patients die of their underlying disease rather than pneumonia. Increased mortality rate is associated with bacteremia with pseudomonas or Acinetobacter species, medical rather than surgical illness and treatment with ineffective antibiotic therapy.

Etiology

HAP, VAP and HCAP are caused by a wide spectrum of bacterial pathogens, and are rarely due to viral or fungal pathogens in immunocompetent hosts. Rate of polymicrobial infection vary widely, but appear to be increasing, and are especially high in patients with adult respiratory distress syndrome (ARDS). Most common pathogens among patients with early onset NP (< 5 days after admission) who have no risk factor for MDR pathogens include Streptococcus pneumoniae, H. influenzae, Methicillin sensitive S. aureus (MSSA) and enteric gram negative bacilli like E. coli, Klebsiella, Proteus and Serratia. These organisms have been designated as core pathogens. There are some risk factors which increase the likelihood for MDR pathogens like methicillin resistant S. aureus

(MRSA), Pseudomonas aeruginosa, Acinetobacter species, Klebsiella pneumoniae, Stenotrophomonas maltophilia, ESBL (extended spectrum beta lactamases) producing enterobacteriaceae. In fact, some organisms (MRSA and K. pneumoniae) are more common in nonventilated than ventilated patients, whereas certain resistant organisms are more common in patients with VAP (P. aeruginosa, Stenotrophomonas maltophilia and Acinetobacter species).

HAP involving anaerobic organisms may follow aspiration in non-intubated patients, but is rare in patients with VAP. Clinical risk factors and comorbidities can also help to identify the likely causative pathogens. Glucocorticoid therapy, malnutrition, structural lung disease and mechanical ventilation are risk factors for P. aeruginosa. S. aureus (including MRSA) is more common among patients in coma or with head trauma, diabetes mellitus, renal failure, prior antibiotic therapy (quinolone and macrolides), enteral feeding, surgery and late onset VAP. Legionella infection usually occurs in immunocompromised patients such as organ transplant recipients or patients with HIV disease. HAP due to legionella species is more common in hospital where water supply is contaminated. Nosocomial pneumonia due to fungi such as candida species and Aspergillus fumigatus may occur in immunocompromised or neutropenic patients, but is uncommon in immunocompetent patients. In fact, colonisation with candida was found to be an independent risk factor for pneumonia, the risk being greatest for P. aeruginosa.⁴ The incidence of VAP and HAP due to virus is also low in immunocompetent hosts. Outbreak of NP due to virus such as influenza, parainfluenza, adenovirus, measles and respiratory syncytial virus have been reported and out of all these viruses influenza A is the most common viral cause of HAP and HCAP in adult patients.

Pathogenesis

HAP occurs when the delicate balance between the host defences and microbial propensity for

Table 2 : Risk factors for nosocomial pneumonia**A. Impaired host defences / Increase aspiration**

- Endotracheal tube
- Supine position
- Impaired mental status
- Sedation
- Nasogastric tube

B. Overgrowth of virulent organisms

- Prolonged antibiotic use
- Iatrogenic (inadequate hand washing)
- Central venous lines
- Frequent hospitalisation
- Prolonged hospital stays
- Contaminated respiratory equipment
- Administration of H₂ receptor antagonist or protein pump inhibitors.

colonisation and invasion shifts in favor of the ability of the pathogens to persist and invade the lower respiratory tract. HAP requires the entry of microbial pathogens into the lower respiratory tract, followed by colonisation, which can then overwhelm the host's mechanical (ciliated epithelium and mucus), humoral (antibody and complement) and cellular (polymorphonuclear leukocytes, macrophages, lymphocytes) defences to establish the infection. Aspiration of oropharyngeal pathogen or leakage of bacteria around the endotracheal tube cuff is the primary route of bacterial entry into the lower respiratory tract. Some investigators postulate that colonisation of the endotracheal tube with the bacteria encased in biofilm may result in embolisation into the alveoli during suctioning or bronchoscopy.⁵ The stomach and sinuses have been suggested as potential reservoirs for certain bacteria colonizing the oropharynx and trachea. Inhalation of pathogens from contaminated aerosol and direct inoculation are less common. Hematogenous spread from infected intravascular catheters is also quite rare. Various risk factors for nosocomial pneumonia are given in Table 2.

Diagnosis

A variety of diagnostic modalities exist, but there is no universally accepted criteria or "gold standard" for diagnosis. A *clinical diagnosis* generally requires presence of new or progressive infiltrate on chest radiograph plus at least two of the following i. e.

- Fever ($> 37.8^{\circ} \text{C}$ / $> 100^{\circ} \text{F}$),
- Leukocytosis ($> 10,000/\mu\text{l}$),
- Production of purulent sputum.

There may be other features like dyspnea, hypoxemia, tachycardia, pleuritic chest pain and findings of consolidation. Clinical diagnosis of NP is sensitive, but not specific and can lead to an antibiotic overuse. If there is clinical suspicion of NP the lower respiratory tract secretion should be collected (either bronchoscopically or nonbronchoscopically) for quantitative culture. Invasive diagnostic strategy for NP generally use bronchoscopy to obtain quantitative culture using a protected specimen brush (PSB) device to limit contamination or bronchoalveolar lavage (BAL). A patient is considered to have nosocomial pneumonia when culture result reveals more than 10³ cfu / ml with PSB or more than 10⁴ cfu / ml with BAL. However, a number of problems are associated with the use of bronchoscopy, the equipment and expertise is not always available and sampling is often followed by a period of hypoxemia. A major concern with bacteriologic approach is that a false negative culture can lead to failure to treat a specific patient or a specific pathogen, and that the results are not always consistent and reproducible. A major factor causing false negative quantitative culture is antibiotic therapy in the preceding 72 hours. A review of 23 studies of BAL in suspected VAP showed a sensitivity of $73 \pm 18\%$ and a specificity of $82 \pm 19\%$.⁶ Pooled data from 18 studies with PSB reveal more sensitivity of 89% and specificity of 94%.⁷ Thus PSB appears to be more specific than sensitive for the presence of pneumonia. Endotracheal aspirate can also be cultured quantitatively and with a threshold of 10⁶ cfu / ml the mean sensitivity and specificity of this method

for the presence of pneumonia is $76 \pm 9\%$, $75 \pm 28\%$ respectively.⁸ Collection of sample for culture of endotracheal aspirate is very simple technic and can be done easily and quickly. Though there is some evidence to suggest that use of this method

Table 3 : Nosocomial Infection Surveillance System Clinical Criteria for the Diagnosis of Pneumonia

Radiographic

Two or more serial chest radiographs with new or progressive and persistent infiltrate or cavitations or consolidation (one radiograph is sufficient in patients without underlying cardiopulmonary disease)

Clinical

One of the following

- Fever $> 38^{\circ} \text{C}$ ($> 100.4^{\circ} \text{F}$) with no other recognised cause
- WBC count $< 4,000/\mu\text{L}$ or $\geq 12,000 / \mu\text{L}$
- For adults ≥ 70 year old, altered mental status with no other recognised cause

And at least two of the following

- New-onset purulent sputum or change in character of sputum, or increase in respiratory secretions or suctioning requirements
- New onset or worsening cough, dyspnea, or tachypnea
- Rales or bronchial breath sounds
- Worsening gas exchange, increased oxygen requirements, increased ventilator support

Microbiology (optional)

Positive culture result (one), blood (unrelated to other source), pleural fluid, quantitative culture by BAL or PSB, $\geq 5\%$ BAL obtained cells contain intracellular bacteria.

has a high false positive rate in the diagnosis of VAP, other studies suggest that quantitative culture of tracheal aspirate offers a reliable alternative to invasive technic.

A clinical diagnosis of NP is likely to lead to antibiotic overuse and bronchoscopic diagnosis is invasive, costly and requires technical expertise. Identifying a diagnostic approach between these extremes is extremely important. A standardised diagnostic algorithm employing clinical and microbiological data are used in the National Nosocomial Infection Surveillance System (NNIS) to facilitate reporting of NP which has been depicted in Table 3. Recently Miller and colleagues compared the NNIS criteria with clinical suspicion confirmed by quantitative culture of BAL in 292 trauma patients.⁹ The NNIS criteria and clinical identification confirmed by BAL had a similar incidence of VAP, confirming the epidemiologic utility of the NNIS criteria. However, when applied to individual patients using BAL result as the standard, the NNIS criteria had a sensitivity of 84% and a specificity of 69%. The clinical pulmonary infection score (CPIS) (which uses microbiological data) or a modified CPIS (which does not use microbiological data) have also been proposed to improve diagnostic consistency among clinicians and investigators. A CPIS > 6 is often regarded as consistent with a diagnosis of pneumonia.¹⁰ The CPIS clinical criteria has been mentioned in Table 4. Unfortunately CPIS has not consistently demonstrated either an improvement in the diagnostic accuracy when used as an adjunct

Table 4 : Clinical Pulmonary Infection Score Clinical Criteria for the Diagnosis of Pneumonia

Variables	Points		
	0	1	2
Temperature, $^{\circ}\text{C}$	≥ 36.1 to ≤ 38.4	≥ 38.5 to ≤ 38.9	≥ 39 to ≤ 36
WBC count / μL	≥ 4000 to ≤ 11000	< 4000 to > 11000	
Secretions:	Absent	Present, Nonpurulent	Present, purulent
Pao_2 /fraction of inspired oxygen	> 240 or ARDS		≤ 240 and no ARDS
Chest radiography	No infiltrate	Diffuse or patchy infiltrate	Localised infiltrate
Microbiology	No or light growth	Moderate or heavy growth; and 1 point for same organism on Gram stain	

in clinical decision making, or reproducibility of scoring when used as a research tool to classify patients.

Attempt to further improve the specificity without losing sensitivity have focused on nonbronchoscopic sampling of the distal airway. This can be achieved by blind mini BAL or blind PSB (using a blind telescopic catheter) in which a catheter is blindly inserted through an endotracheal tube to sample distal airway. The sensitivity and specificity of blind mini BAL is 63-100% and 66-96% respectively. The sensitivity and specificity of blind PSB is 58-86% and 71 to 100% respectively. In general, these technics provide data similar to those samples collected bronchoscopically.

Apart from bacteriological study of the lower respiratory tract samples all patients should have a chest radiograph, preferably posteroanterior and lateral, measurement of arterial oxygen saturation, and complete blood count, serum electrolytes, liver and renal function tests to assess any organ dysfunction.

Recommendation for Bacteriological strategy

Quantitative culture of endotracheal aspirate or sample collected either bronchoscopically (i.e. BAL/PSB) or non-bronchoscopically should be performed before starting antibiotic therapy. The choice of method depends on local expertise, experience, availability and cost.

Biological Markers for Diagnosis

There are some studies on biological markers for diagnosis of nosocomial pneumonia. One recent study has revealed that combined measurement of serum procalcitonin and bronchoalveolar fluid level of soluble triggering receptor expressed on myeloid cells (STREM-1) is very useful in differentiating nosocomial pneumonia from extra pulmonary nosocomial infection.¹¹

Antibiotic Treatment Strategy

Optimal management of the patient with suspected VAP requires prompt initiation of appropriate antimicrobial therapy and general supportive care. Several studies show that delay in administration of effective therapy is associated with an increase in mortality rate. Hence as per the recent guidelines, empirical antibiotic therapy must be started promptly after collecting sample of lower respiratory tract secretion. The key decision in initiating empirical therapy depends on the presence of risk factor for MDR organisms. Patients not having risk factor or MDR pathogen can be categorised as low risk patients and patients having any risk factor for MDR pathogens can be categorised as high risk.

Low Risk Patients

In these patients only one antibiotic should be used to target the common community acquired organisms in addition to *S. aureus* and the enterobacter species. So appropriate initial selection would be one of the following antibiotics.

A non-pseudomonal 3rd generation cephalosporin (e.g. Ceftriaxone 1 gm IV/d) or Respiratory quinolone (Levofloxacin 500 mg/d I.V.) or Moxifloxacin 400 mg/d I.V. or Gatifloxacin 400 mg/d I.V.) or Ampicillin / Sulbactam (750-1500 mg I.V. 6 hrly / 8 hrly) or Ertapenem (1 gm IV/ d)

High risk Patients

Patients having risk factor for MDR pathogen (as mentioned in Table 1) should receive combination of antibiotic active against gram negative organisms like *Pseudomonas* and *Acinetobacter*. This requires the use of following combination of antibiotics.

Antipseudomonal Cephalosporin	Cefepime 1-2 gm b.d. or 8 hourly I.V., Ceftazidime – 2 gm 8 hourly I.V.
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Or

Antipseudomonal Carbapenem	Imipenem – 0.5 gm 6 hrly or 1 gm 8 hrly, Meropenem – 1 gm every 8 hourly
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Or	
β-lactam / β-lactamase inhibitor	Piperacillin – tazobactam 4.5 gm every 6 h
Plus	
Antipseudomonal fluoroquinolone	Levofloxacin – 750 mg I.V./d Ciprofloxacin – 500 mg every 12 h
Or	
Aminoglycoside	Gentamicin – 7 mg/kg/d, Tobramycin – 7 mg / kg/d, Amikacin – 20 mg/kg/ d
Plus	
Antibiotic effective against MRSA if risk for MRSA is present)	Vancomycin – 15 mg / Kg every 12 h, Linezolid – 600 mg every 12 h

If risk factor for MRSA is present (like previous treatment with quinolone or macrolides, previous hospitalisation enteral feeding, surgery or late onset VAP) or there is a high incidence locally, a third antibiotic like Vancomycin or Linezolid can also be added to the combination of antibiotic regimen effective against resistant gram negative bacteria. Other antibiotics found effective against MRSA are Quinupristin – dalfopristin and Tigecycline. Tigecycline not only covers MRSA, but also covers Enterobacter (including ESBL phenotype), Acinetobacter and Stenotrophomonas maltophilia, but not effective against pseudomonas.¹² Whenever legionella is suspected the combination of antibiotic regimen should include a macrolide (e.g. Azithromycin) or a fluoroquinolone (e.g. Ciprofloxacin or Levofloxacin) rather than aminoglycoside. Ertapenem has a good in vitro activity against many common anaerobic and aerobic gram positive and gram negative bacteria, but not effective against acinetobacter and

pseudomonas, hence only suitable for low risk patients, but not high risk patients.¹³ Selection of antibiotic treatment also depends on local pattern of antimicrobial susceptibility and should also take into account recently received antibiotic therapy. An effort should be made to use an agent from a different antibiotic class, because recent therapy can predispose to resistance to the same class of antibiotic.

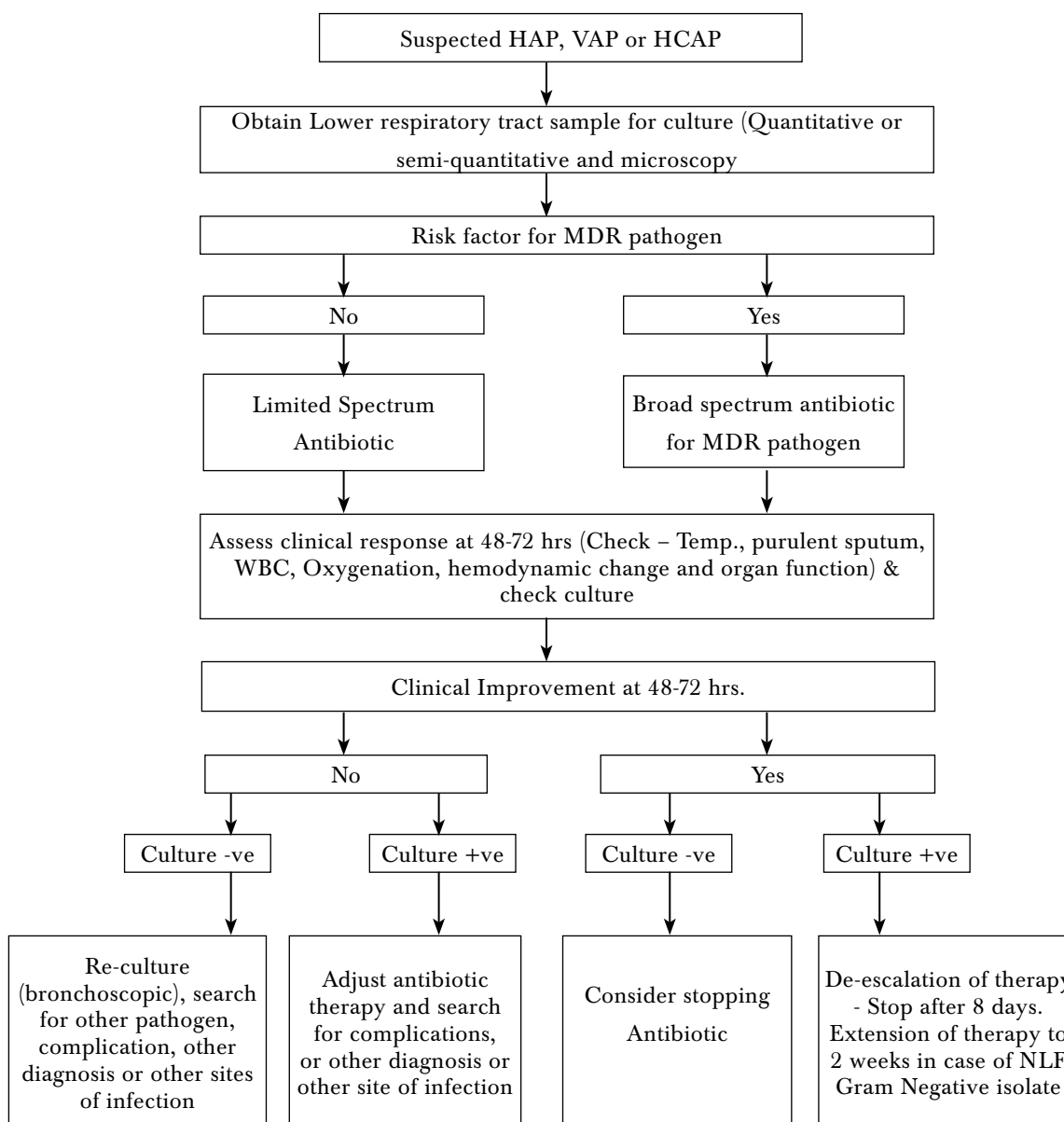
After starting antibiotic therapy, patients should be assessed for clinical improvement at 48-72 hours. If there is clinical improvement and culture report is positive "de-escalation of therapy" should be started, i.e. narrowing the therapy depending on the culture report and limiting the duration of therapy from traditional 14 to 21 days to periods as short as 7 days except for patients with non-fermenting gram negative bacilli (e.g. Pseudomonas and Acinetobacter). A multicentric randomised controlled trial demonstrated that patients who received appropriate initial empiric therapy of VAP for 8 days had outcomes similar to those of patients who received therapy for 14 days except that trend towards greater rates of relapse for short duration therapy was seen if the etiologic agent was Acinetobacter species or P. aeruginosa.¹⁴ So patients infected with non-fermenting gram negative bacilli may need a longer duration of treatment (2 weeks).

A sterile culture in respiratory secretion in the absence of antibiotic in the past 72 hours virtually rules out the presence of pneumonia, but viral and legionella infection is still possible. If these culture negative patients have clinical improvement at 48-72 hours, one can consider stopping the antibiotic therapy. If there is no improvement, then one should collect bronchoscopic sample for re-culture and search for other site of infection or other diagnosis. Algorithm for management of a case of NP is mentioned below.

Selected Key Recommendations

HCAP is included in the spectrum of NP and patients with HCAP need therapy for MDR pathogens.

ALGORITHM FOR MANAGEMENT OF NOSOCOMIAL PNEUMONIA



Sample of lower respiratory tract secretions should be obtained from all patients with suspected NS before starting empiric antibiotic therapy. Samples can include an endotracheal aspirate, bronchoalveolar lavage or protected specimen brush sample and can be cultured quantitatively or semi-quantitatively.

Early appropriate empiric antibiotic therapy must be started in sufficient dose. The empirical therapy depends mostly on presence of risk factor

for MDR pathogen.

Clinical response and culture should be assessed at 48 – 72 hrs and in case of clinical improvement, but negative culture report, one can consider discontinuing antibiotic therapy.

De-escalation of antibiotics should be started once the culture report is available. A shorter duration of antibiotic therapy (7-8 days) is recommended for patients with uncomplicated HAP, VAP, or

HCAP who have good clinical response except in patients with non-fermenting gram negative bacilli where therapy for longer duration (2 weeks) is advisable.

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